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1   **Title page**

2   **Full title**

3   Impact of antibiotic treatment duration on outcomes in older men with suspected  
4   urinary tract infection: retrospective cohort study

5   **Running title**

6   Antibiotic duration for UTI in older men

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18   **Keywords**

19   Urinary tract infection; aged; electronic health records; primary care; men

20   **Key points**

- 21       • Clinical guidelines recommend at least seven days of antibiotic treatment for  
22       urinary tract infection in men, but this is largely based on expert opinion.
- 23       • It is not known if shorter durations of antibiotic treatment are as safe or effective  
24       as seven days.

- We used linked health data from the UK to estimate the risk of treatment failure, hospitalisation and death in older men presenting to primary care with suspected urinary tract infection, who were prescribed different durations of antibiotic treatment.
- We found that 3-day antibiotic treatment was associated with an increased risk of treatment failure but a reduced risk of acute kidney injury.
- These findings support the need for a definitive randomised trial of short versus standard duration treatment.

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#### **Prior presentation of this work**

Findings from this research were presented at the General Practice Research in Infections Network meeting in Utrecht, The Netherlands, on 5<sup>th</sup> October 2018.

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## 48 **Abstract**

### 49 **Purpose**

50 Clinical guidelines recommend at least seven days of antibiotic treatment for older  
51 men with urinary tract infection (UTI). There may be potential benefits for patients,  
52 health services and antimicrobial stewardship if shorter antibiotic treatment resulted in  
53 similar outcomes. We aimed to determine if treatment duration could be reduced by  
54 estimating risk of adverse outcomes according to different prescription durations.

### 55 **Methods**

56 This retrospective cohort study included men aged  $\geq 65$  years with a suspected UTI.  
57 We compared outcomes in men prescribed 3, 5, 7 and 8-14 days of antibiotic treatment  
58 in a multivariable logistic regression analysis, and 3 versus 7 days in a propensity-  
59 score matched analysis. Our outcomes were re-consultation and re-prescription  
60 (proxy for treatment failure), hospitalisation for UTI, sepsis, or acute kidney injury  
61 (AKI), and death.

### 62 **Results**

63 Of 360,640 men aged  $\geq 65$  years, 33,745 (9.4%) had a UTI. Compared to 7-days, men  
64 prescribed 3-day treatment had greater odds of re-consultation and re-prescription  
65 (adjusted OR 1.48, 95% CI 1.25-1.74) but lower odds of AKI hospitalisation (adjusted  
66 OR 0.66, 95% CI 0.45-0.97). We estimated that treating 150 older men with 3-days  
67 instead of 7-days of antibiotics could result in four extra re-consultation and re-  
68 prescriptions and one less AKI hospitalisation. We estimated annual prescription cost  
69 savings at around £2.2 million.

### 70 **Conclusions**

71 Antibiotic treatment for older men with suspected UTI could be reduced to 3-days,  
72 albeit with a small increase in risk of treatment failure. A definitive randomised trial is  
73 urgently needed.

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## **Main text**

### **Introduction**

Urinary tract infections (UTIs) represent an important cause of morbidity and antibiotic use in older men. Around 20% of all UTIs occur in men.<sup>1</sup> Incidence increases with age from around 3 episodes per 100 person-years in men aged 65-74, to 8-11 episodes per 100 person-years in men aged  $\geq 85$ .<sup>2, 3</sup>

The optimal duration of antibiotic treatment for UTI in older men is not known.<sup>4</sup> Most clinical guidelines recommend seven days of antibiotic treatment.<sup>5-7</sup> This recommendation is largely based on expert consensus due to the lack of data in this area. Previous randomised trials investigating different antibiotic durations for UTI in men have focussed on febrile<sup>8, 9</sup> or complicated UTI,<sup>10, 11</sup> or men with spinal cord injury,<sup>12</sup> and are not generalizable to the majority of men with community-acquired UTI seen and treated in primary or ambulatory care settings.

Antimicrobial stewardship policies and guidelines recommend prescribing the minimum duration of antibiotic treatment required for clinical resolution.<sup>13, 14</sup> Two recent studies indicate that antibiotic treatment duration for UTI in older men could be reduced. First, a retrospective study of UK health records found that around 20% of older men presenting to primary care with a UTI were prescribed  $< 7$  days of antibiotics, suggesting that some clinicians may already be prescribing shorter treatment to selected men.<sup>2</sup> Second, an observational study found no difference in the rate of clinical recurrence between US male Veterans with UTI prescribed long course ( $> 7$  days) versus short course treatment ( $\leq 7$  days).<sup>15</sup> However, this study used outpatient data only and therefore may have missed men who were subsequently hospitalised with UTI-related emergencies, such as sepsis or acute kidney injury.

We therefore used anonymised linked health records that spanned primary care, secondary care and death registry data, to estimate risk of adverse outcomes in older men prescribed different durations of antibiotic treatment for UTI in primary care. Our aim was to assess whether short course treatment was associated with an increased risk of adverse events to determine the potential for safe and effective reduction of antibiotic treatment duration.

## **Patients and Methods**

### **Data Source**

We used the Clinical Practice Research Datalink (CPRD), an electronic database of anonymised primary care records, covering 11.3 million patients from 674 general practices across the UK.<sup>16</sup> Approximately 7% of the UK population are included and patients are broadly representative of the wider UK population in terms of age, gender and ethnicity. The CPRD holds data on demographics, clinical encounters and diagnoses (coded using Read codes), drug prescriptions, laboratory tests and referrals to specialists. Data are available once the primary care records have met a series of quality checks on completeness and reliability and the CPRD deems them to be of a required standard for research purposes. Linked hospital and death registration data are available for patients from approximately 50% of contributing English practices. Hospital diagnoses and causes of death are recorded using version 10 of the International Classification of Disease (ICD-10).

The CPRD Independent Scientific Advisory Committee approved the study protocol (protocol number 17\_250). Further ethical approval was not required as the proposed research was within the remit of the CPRD's broad National Research Ethics Service approval. We used the Reporting of Studies Conducted using Observational

Routinely-collected Health Data (RECORD) statement and checklist to guide study reporting.<sup>17</sup>

## **Design and participants**

This was a retrospective cohort study using linked health record data. Men were eligible for inclusion if, between 1<sup>st</sup> January 2010 and 31<sup>st</sup> December 2016, their data were of the quality required by CPRD, they were  $\geq 65$  years old, were registered with a practice that had consented to linkage to hospital and death registry data, and had a primary care record of an incident UTI. Follow-up began from the latest of, study start date (1<sup>st</sup> January 2010), patient's 65<sup>th</sup> birthday, six months after they registered with the practice (to avoid including historical UTIs recorded at registration), or the date their practice met the CPRD data quality requirements. Follow-up ended on the earliest of study end date (31<sup>st</sup> December 2016), the day the patient died or transferred out of the practice (i.e. last date of CPRD data collection), or 28 days after an incident UTI event. We excluded men who were temporary residents, or had gaps in their data coverage. We defined 'incident' as an event occurring in a man without a UTI-related Read code or trimethoprim or nitrofurantoin prescription in the preceding 90 days. We defined UTI as the presence of a symptom code (e.g., "dysuria") or diagnostic code (e.g., "cystitis") relevant to UTI (codes available in Supplementary Appendix 1), and a same-day prescription code indicating prescribing of a relevant antibiotic. We restricted the analyses to the first incident UTI identified during a patient's follow-up period.

## **Exposure**

We used prescription data for daily dosing and total quantity prescribed to calculate duration of antibiotic prescriptions as a proxy for duration of treatment. We excluded



prescriptions with durations >14 days as it is unlikely that these were prescribed for an acute UTI, and more likely that they reflected treatment for prostatitis. We also excluded prescription durations of 1, 2, 4, and 6 days, as together these represented <1% of all calculated durations and were potentially unreliable. The final exposure groups were 3, 5, 7 and 8-14 days.

## **Outcomes**

We assessed the impact of antibiotic prescription duration on:

1. Re-consultation for urinary symptoms and a same-day antibiotic prescription within 14 days following the incident UTI, as a proxy for treatment non-response, ascertained through Read and prescription codes recorded in primary care records.
2. Hospitalisation for UTI, sepsis, or acute kidney injury (AKI) within 14 days following the incident UTI ascertained from ICD-10 codes recorded in linked hospital admission data for the first episode of a hospital admission, i.e., the episode most likely responsible for the admission.
3. Death within 28 days following the incident UTI using linked death registration data.

## **Statistical Analyses**

We used primary care demographic and clinical codes to describe baseline characteristics for patients by prescription duration. Firstly, we assessed the impact of different prescription durations by calculating odds ratios (OR) and 95% confidence intervals (CI) for the risk of each outcome in those prescribed 7-day treatment, compared to those prescribed 3, 5 or 8-14 days treatment. We adjusted for potential confounders of the association between antibiotic duration and outcome, including the

choice of antibiotic, age, Index of Multiple Deprivation score quintile, Charlson comorbidity score, polypharmacy (defined as records indicating  $\geq 5$  long-term medications per month in the year prior to the incident UTI), and the presence or absence of a record indicating diabetes, dementia, coronary heart disease, stroke, cancer, heart failure, renal disease, benign prostatic hyperplasia, and prostate cancer.

Secondly, we compared outcomes in men prescribed 3-day versus 7-day treatment using propensity score matching to improve balance of baseline covariates across the two treatment groups. We chose 7 days as the reference standard as it is currently the recommended treatment duration for male UTI in the UK, and 3 days as the comparator as it is a potentially acceptable and feasible shorter duration of treatment, given that 3-day treatment is widely used to treat UTI in women. Men were matched on a range of demographic and clinical variables related to their propensity to receive a 7-day prescription. We used nearest neighbour matching with no replacement and matched each patient with a 3-day prescription to three patients with a 7-day prescription. We assessed balance in measured baseline covariates between matched groups by visually inspecting jitter plots and histograms of covariate distribution before and after matching, and by calculating standardised mean differences for covariates between groups. We regarded standardised mean differences of  $<0.1$  as reflecting adequate balance.<sup>18, 19</sup>

We used mixed effects models in both analyses to account for clustering by general practice. We repeated the analyses restricting to men prescribed trimethoprim, the most commonly used antibiotic for UTI in the UK during the study period. Finally, we calculated E-values to estimate the minimum effect size required by an unmeasured confounder to fully explain away any statistically significant associations.<sup>20</sup> All statistical tests were 2-sided with  $p < 0.05$  considered statistically significant but an

effect size of 10% considered clinically significant. Analyses were conducted in R version 3.2.1.

## Results

From a cohort of 360,640 men aged 65 and over with a median follow-up of 4.9 years (Interquartile range (IQR), 3.1-6.4), we identified 33,745 (9.4%) with an incident UTI treated with a relevant antibiotic (Figure 1). Of these, we were able to assign an antibiotic prescription duration to 32,593 (96.6%) incident UTIs. The median age at the time of incident UTI was 77 years (IQR, 70 - 83). In total, 1966 (6.0%) men were prescribed amoxicillin, 2002 (6.1%) ciprofloxacin, 2060 (6.3%) cefalexin, 2143 (6.6%) co-amoxiclav, 5724 (17.6%) nitrofurantoin, and 18,698 (57.4%) trimethoprim. Guideline concordant 7-day treatment was prescribed to 20,729 (63.6%) men, 3-day treatment to 2498 (7.7%), 5-day treatment to 6254 (19.2%), and 8-14 days to 3112 (9.5%). Practices varied in their prescribing of the different antibiotic durations. Of all antibiotic prescriptions for UTI in older men, the median proportion prescribed 3-day treatment was 5.1% (IQR, 1.8-10.8), 5-day treatment was 14.6% (IQR, 7.7-25.4), 7-day treatment was 65.4% (IQR, 53.1-76.2), and >7day treatment was 8.3% (IQR, 3.8-14.8). Baseline comorbidities were broadly similar across the different treatment duration groups (Table 1).

## Outcomes according to treatment duration

A total of 2007 (6.2%) men re-consulted and received another antibiotic prescription within 14 days following the incident UTI. Compared to 7-day prescriptions, there was a graded association between prescription duration and odds of re-consultation and re-prescription with adjusted ORs of 1.48 (95% CI 1.25-1.74) for 3-day prescriptions, 1.18 (95% CI 1.04-1.33) for 5-day prescriptions, and 0.80 (95% CI 0.67-0.96) for 8-14

day prescriptions (Table 2). The re-prescribed antibiotics were made up of a lower proportion of trimethoprim, similar proportion of amoxicillin, and greater proportions of the other antibiotics (Supplementary Table 1).

A total of 817 (2.5%) men were hospitalised for UTI, 89 (0.3%) hospitalised for sepsis, and 449 (1.4%) hospitalised for AKI within 14 days following the incident UTI. There were no significant associations between antibiotic prescription duration and hospitalisation for UTI or sepsis. Compared to 7-days, 3 and 8-14 day prescriptions were associated with reduced odds of hospitalisation for AKI (adjusted OR for 3-days, 0.66, 95% CI 0.45-0.97, adjusted OR for 8-14 days, 0.63, 95% CI 0.40-0.99). A total of 419 (1.3%) men died within 28 days of the incident UTI. There were no significant associations between antibiotic prescription duration and odds of death.

### **Propensity score matched comparison of 7-day versus 3-day therapy**

We matched 2392 men prescribed 3-day treatment to 7182 men prescribed 7-day treatment. Inspection of jitter plots and histograms suggested matching had improved balance of covariates across the two groups. Standardised mean differences were all less than 0.1 (Table 3). 3-day prescriptions were associated with increased odds of re-consultation and re-prescription (OR 1.52, 95% CI 1.25-1.85) and reduced odds of hospitalisation for AKI (OR 0.62, 95% CI 0.42-0.93) (Table 4).

Using the propensity score matched event rates and ORs in table 4, we estimate that treating 150 older men with 3-day instead of 7-day treatment, could result in four extra re-consultation and re-prescriptions (numbers needed to harm = 37) and one less AKI hospital admission (numbers needed to treat = 148).<sup>22</sup> Our previous study showed that around 7% of a sample of roughly 400,000 men  $\geq 65$  were prescribed an antibiotic in primary care for UTI in 2014.<sup>2</sup> Current UK population estimates suggest there are

around 5.2 million men aged  $\geq 65$ .<sup>23</sup> A 7% annual UTI rate equates to around 364,000 UTI events. Based on current prescribing costs reported in the British National Formulary (3-day trimethoprim = £3.60, 7-day trimethoprim = £10.00, 7-day nitrofurantoin = £9.50), if all men were prescribed 3-days of trimethoprim instead of 7 days, and men who re-consulted were prescribed 7 days of nitrofurantoin, the UK health service could save around £2.2 million a year.

### **Sensitivity analyses**

We repeated the analyses restricting to men who received trimethoprim and found that all ORs were consistent with our main analyses. We calculated E-values for the two significant associations in our propensity-score matched analysis. The E-value was 2.4 for re-consultation and re-prescription, and 2.6 for AKI hospitalisation, suggesting any unmeasured confounder would require an OR of at least 2.4 for its association with antibiotic prescription duration and outcome, independent of measured confounders, to explain away the observed associations.

### **Discussion**

We showed, for the first time, that in older men presenting to primary care with a UTI, 3-day antibiotic treatment was associated with a 52% increase in odds of re-consultation and re-prescription that may indicate treatment failure or recurrent infection, but was not associated with increased odds of UTI-related hospitalisation or death. We also showed for the first time, an association between 3-day treatment and a 38% reduction in the odds of hospitalisation for AKI.

### **Results in context**

A retrospective observational study of 33,336 index UTIs in US male Veterans found no difference in recurrence rates at 30 days between short and long duration antibiotic

treatment.<sup>15</sup> Similar to our study, patients did not require microbiological confirmation of UTI and were included if they had a relevant diagnostic code and antibiotic prescription. However, this study defined 'short duration' as  $\leq 7$  days, and 77% of the short duration group received 7-day treatment. Thus, their comparison was  $\leq 7$  days versus  $> 7$  days, and explains the discrepancy between our finding of increased odds of re-consulting and receiving another antibiotic prescription in short duration (3 or 5-day) versus long duration (7-day) treatment.

Our finding of an association between 3-day antibiotic treatment and reduced odds of AKI could be explained by trimethoprim prescribing. Trimethoprim is associated with hyperkalaemia and AKI in older adults.<sup>21</sup> In our unmatched multivariable logistic regression analysis, the risk of AKI was reduced in the group with the shortest exposure to trimethoprim (3-day treatment) and the group with the lowest proportion of trimethoprim use (8-14 day group, 16.8% prescribed trimethoprim versus 60% in the 7-day group). In our propensity-score matched analysis, 85% of men in the 3 and the 7-day treatment groups were prescribed trimethoprim, but there was again a reduced risk of AKI in the 3-day group, supporting an association between shorter trimethoprim exposure and reduced risk of AKI.

Few randomised trials have investigated the potential for shorter duration of antibiotic treatment in men with UTI, and those that have focussed on more severe UTI. A Swedish trial of 114 men with febrile UTI showed similar clinical and microbiological cure rates between 14-day and 28-day antibiotic treatment.<sup>9</sup> A randomised placebo controlled non-inferiority trial recruited men with febrile UTI from Dutch primary care and emergency departments, and showed 7-day antibiotic treatment was inferior to 14-day treatment in terms of clinical cure rates 10-18 days post UTI.<sup>8</sup> In contrast, a US trial of men and women (39% men) with complicated UTI or acute pyelonephritis

showed no difference in outcomes between those receiving 5-day versus 10-day antibiotic treatment.<sup>10</sup> However, these trials recruited men with more severe UTI than that normally seen in a primary care setting. To the best of our knowledge, no trials have investigated the effect of short duration antibiotic treatment for men presenting to primary care with symptoms suggestive of UTI, but without fever or other signs of ascending infection.

### **Strengths and weaknesses of this study**

We used data from a general practice database that is broadly representative of the UK population.<sup>16</sup> Cohort entry was dependent on presentation and empirical treatment of UTI in primary care, and thus reduced indication bias. We also reduced indication bias by matching patients on their propensity to receive a 7-day prescription, and achieving adequate balance of covariates across treatment groups.

Our study has important limitations. We attempted to capture patients presenting with UTI but had no microbiological data to support this. However, whilst a limitation, this is also more representative of clinical practice. Our estimates are based on *prescription* duration and may overestimate actual antibiotic consumption. Despite careful selection of codes used to identify eligible men, differential use of codes amongst clinicians means we may have included some men who had more complicated UTI or pyelonephritis. Our finding of an increase in the rate of UTI-related re-consultation and re-prescription among men prescribed 3-day treatment may be due to planned follow-up for those prescribed shorter courses. Furthermore, whilst some of these events may represent ‘treatment failure’, others may reflect different expectations about the speed of symptom resolution. Finally, despite our design, differential coding, indication bias and residual confounding may still have affected our

findings. However, our E-values suggest residual confounders would need relatively strong associations between antibiotic duration and outcomes to alter the conclusions from our effect estimates.

## **Conclusions**

Our findings suggest it may be possible to safely reduce the duration of antibiotic treatment to 3 days for older men presenting to primary care with a UTI. For patients, shorter duration treatment could mean better adherence and less side effects. Other potential benefits may include a reduction in AKI-related hospitalisations, antibiotic burden, and prescription costs. Potential harms include a possible increased risk of treatment failure. A definitive randomised trial is needed to compare short versus standard treatment duration of a specific antibiotic for UTI in men.



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## **Transparency declaration**

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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468 **Tables**

469 Table 1. Baseline characteristics according to antibiotic prescription duration. Values  
470 are numbers (%) unless otherwise stated.

	Antibiotic prescription duration			
	3 days	5 days	7 days	8-14 days
<b>Number (%) of prescriptions</b>	2498 (7.7)	6254 (19.2)	20729 (63.6)	3112 (9.5)
<b>Mean (SD) age</b>	77.4 (8.0)	77.7 (8.1)	76.9 (7.9)	76.7 (7.8)
<b>Antibiotic choice</b>				
Amoxicillin	12 (0.5)	512 (8.2)	1392 (6.7)	50 (1.6)
Cefalexin	60 (2.4)	262 (4.2)	1133 (5.5)	605 (19.4)
Ciprofloxacin	38 (1.5)	852 (13.6)	649 (3.1)	463 (14.9)
Co-amoxiclav	13 (0.5)	195 (3.1)	1843 (8.9)	92 (3.0)
Nitrofurantoin	241 (9.6)	802 (12.8)	3301 (15.9)	1380 (44.3)
Trimethoprim	2134 (85.0)	3631 (58.1)	12411 (59.9)	522 (16.8)
<b>Index of multiple deprivation decile</b>				
1 or 2 (least deprived)	527 (21.1)	1670 (26.7)	5217 (25.2)	890 (28.6)
3 or 4	552 (22.1)	1494 (23.9)	5016 (24.2)	764 (24.6)
5 or 6	599 (24.0)	1398 (22.4)	4568 (22.0)	655 (21.0)
7 or 8	427 (17.1)	945 (15.1)	3437 (16.6)	466 (15.0)
9 or 10 (most deprived)	393 (15.7)	747 (11.9)	2491 (12.0)	337 (10.8)
<b>Housebound</b>	101 (4.0)	251 (4.0)	641 (3.1)	107 (3.4)
<b>Respiratory disease</b>	478 (19.1)	1159 (18.5)	3934 (19.0)	629 (20.2)
<b>Cardiac failure</b>	178 (7.1)	438 (7.0)	1365 (6.6)	202 (6.5)
<b>Dementia</b>	160 (6.4)	399 (6.4)	1080 (5.2)	158 (5.1)
<b>Peripheral vascular disease</b>	218 (8.7)	573 (9.2)	1695 (8.2)	248 (8.0)
<b>Renal disease</b>	620 (24.8)	1560 (24.9)	4758 (23.0)	755 (24.3)
<b>Rheumatoid arthritis</b>	47 (1.9)	105 (1.7)	374 (1.8)	53 (1.7)
<b>Cancer</b>	486 (19.5)	1306 (20.9)	4225 (20.4)	689 (22.1)
<b>Stroke</b>	320 (12.8)	856 (13.7)	2542 (12.3)	370 (11.9)
<b>Diabetes</b>	576 (23.1)	1411 (22.6)	4659 (22.5)	677 (21.8)
<b>Liver disease</b>	17 (0.7)	36 (0.6)	122 (0.6)	23 (0.7)
<b>Ischaemic heart disease</b>	674 (27.0)	1622 (25.9)	5347 (25.8)	811 (26.1)
<b>Urinary catheter</b>	182 (7.3)	626 (10.0)	1783 (8.6)	325 (10.4)
<b>Urinary incontinence</b>	184 (7.4)	496 (7.9)	1393 (6.7)	225 (7.2)
<b>Polypharmacy</b>	1048 (42.0)	2462 (39.4)	7859 (37.9)	1123 (36.1)
<b>Benign prostatic hyperplasia</b>	760 (30.4)	1953 (31.2)	6341 (30.6)	1033 (33.2)
<b>Prostate cancer</b>	213 (8.5)	626 (10.0)	2071 (10.0)	331 (10.6)
<b>eGFR</b>				
60-90	1569 (62.8)	3909 (62.5)	13573 (65.5)	2016 (64.8)
45-59	514 (20.6)	1269 (20.3)	4101 (19.8)	600 (19.3)
30-44	223 (8.9)	563 (9.0)	1735 (8.4)	280 (9.0)
15-29	69 (2.8)	201 (3.2)	478 (2.3)	93 (3.0)
<15	19 (0.8)	48 (0.8)	74 (0.4)	11 (0.4)
missing	104 (4.2)	264 (4.2)	768 (3.7)	112 (3.6)

Charlson score				
0	657 (26.3)	1594 (25.5)	5819 (28.1)	836 (26.9)
1	484 (19.4)	1254 (20.1)	4067 (19.6)	579 (18.6)
2	512 (20.5)	1230 (19.7)	3958 (19.1)	613 (19.7)
3	334 (13.4)	902 (14.4)	2881 (13.9)	450 (14.5)
4	219 (8.8)	522 (8.3)	1759 (8.5)	258 (8.3)
5	141 (5.6)	351 (5.6)	1131 (5.5)	189 (6.1)
≥6	151 (6.0)	401 (6.4)	1114 (5.4)	187 (6.0)

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Table 2. Adjusted ORs and 95% CIs for each outcome by antibiotic prescription duration.

<b>Re-consultation and re-prescription within 14 days</b>	<b>Number of prescriptions</b>	<b>Number (%) of events</b>	<b>Crude OR</b>	<b>Adjusted OR (95% CI)</b>	<b>p-value</b>
7 days [reference]	20729	1225 (5.9)	1	1	
3 days	2498	198 (7.9)	1.37	1.48 (1.25 - 1.74)	<0.001
5 days	6254	416 (6.7)	1.13	1.18 (1.04 - 1.33)	0.009
8-14 days	3112	168 (5.4)	0.91	0.80 (0.67 - 0.96)	0.020
<b>Hospitalised for UTI within 14 days</b>					
7 days [reference]	20729	543 (2.6)	1	1	
3 days	2498	61 (2.4)	0.93	0.87 (0.66 - 1.15)	0.331
5 days	6254	147 (2.4)	0.89	0.82 (0.67 - 1.01)	0.063
8-14 days	3112	66 (2.1)	0.81	0.81 (0.61 - 1.08)	0.152
<b>Hospitalised for sepsis within 14 days</b>					
7 days [reference]	20729	53 (0.3)	1	1	
3 days	2498	4 (0.2)	0.63	0.63 (0.22 - 1.75)	0.366
5 days	6254	13 (0.2)	0.81	0.63 (0.34 - 1.19)	0.159
8-14 days	3112	9 (0.3)	1.13	0.85 (0.38 - 1.90)	0.700
<b>Hospitalised for AKI within 14 days</b>					
7 days [reference]	20729	307 (1.5)	1	1	
3 days	2498	30 (1.2)	0.82	0.66 (0.45 - 0.97)	0.033
5 days	6254	88 (1.4)	0.97	0.84 (0.66 - 1.08)	0.182
8-14 days	3112	24 (0.8)	0.53	0.63 (0.40 - 0.99)	0.047
<b>Death within 28 days</b>					
7 days [reference]	20729	252 (1.2)	1	1	
3 days	2498	37 (1.5)	1.22	1.12 (0.78 - 1.61)	0.522
5 days	6254	89 (1.4)	1.17	1.01 (0.78 - 1.31)	0.917
8-14 days	3112	41 (1.3)	1.08	1.21 (0.83 - 1.78)	0.316

Table 3. Baseline characteristics before and after propensity-score matching of men prescribed three versus seven days of antibiotics. Values are numbers (%) unless otherwise stated. \*SMD = standardised mean difference

	Before matching			After matching		
	3 days	7 days	SMD*	3 days	7 days	SMD*
<b>Number (%) of prescriptions</b>	2498 (7.7)	20729 (63.6)		2394 (25.0)	7182 (75.0)	
<b>Mean (SD) age</b>	77.4 (8.0)	76.9 (7.9)	0.071	77.5 (8.0)	77.4 (8.0)	0.008
<b>Antibiotic choice</b>						
Amoxicillin	12 (0.5)	1392 (6.7)	-0.887	12 (0.5)	39 (0.5)	-0.006
Cefalexin	60 (2.4)	1133 (5.5)	-0.202	57 (2.4)	166 (2.3)	0.005
Ciprofloxacin	38 (1.5)	649 (3.1)	-0.127	38 (1.6)	109 (1.5)	0.006
Co-amoxiclav	13 (0.5)	1843 (8.9)	-1.141	13 (0.5)	36 (0.5)	0.006
Nitrofurantoin	241 (9.6)	3301 (16.0)	-0.217	231 (9.6)	703 (9.8)	-0.005
Trimethoprim	2134 (85.4)	12411 (60.0)	0.727	2043 (85.3)	6129 (85.3)	0.000
<b>IMD decile</b>						
1 or 2 (least deprived)	527 (21.1)	5217 (25.2)		498 (20.8)	1497 (20.8)	
3 or 4	552 (22.1)	5016 (24.2)		529 (22.1)	1545 (21.5)	
5 or 6	599 (24.0)	4568 (22.0)		578 (24.1)	1703 (23.7)	
7 or 8	427 (17.1)	3437 (16.6)		408 (17.0)	1368 (19.0)	
9 or 10 (most deprived)	393 (15.7)	2491 (12.0)	0.147	381 (15.9)	1069 (14.9)	0.000
<b>Housebound</b>	101 (4.0)	641 (3.1)	0.052	100 (4.2)	296 (4.1)	0.003
<b>Respiratory disease</b>	478 (19.1)	3934 (19.0)	0.002	460 (19.2)	1371 (19.1)	0.003
<b>Cardiac failure</b>	178 (7.1)	1365 (6.6)	0.025	178 (7.4)	527 (7.3)	0.004
<b>Dementia</b>	160 (6.4)	1080 (5.2)	0.044	151 (6.3)	469 (6.5)	-0.009
<b>Peripheral vascular disease</b>	218 (8.7)	1695 (8.2)	0.018	213 (8.9)	622 (8.7)	0.008
<b>Renal disease</b>	620 (24.8)	4758 (23.0)	0.047	618 (25.8)	1764 (24.6)	0.029
<b>Rheumatoid arthritis</b>	47 (1.9)	374 (1.8)	-0.002	44 (1.8)	129 (1.8)	0.003
<b>Cancer</b>	486 (19.5)	4225 (20.4)	-0.022	476 (19.9)	1408 (19.6)	0.007
<b>Stroke</b>	320 (12.8)	2542 (12.3)	0.023	319 (13.3)	935 (13.0)	0.009
<b>Diabetes</b>	576 (23.1)	4659 (22.5)	0.020	576 (24.1)	1692 (23.6)	0.012
<b>Liver disease</b>	17 (0.7)	122 (0.6)	0.016	17 (0.7)	51 (0.7)	0.000
<b>Ischaemic heart disease</b>	674 (27.0)	5347 (25.8)	0.028	667 (27.9)	1983 (27.6)	0.006
<b>Urinary catheter</b>	182 (7.3)	1783 (8.6)	-0.053	174 (7.3)	498 (6.9)	0.013
<b>Urinary incontinence</b>	184 (7.4)	1393 (6.7)	0.018	175 (7.3)	512 (7.1)	0.007
<b>Polypharmacy</b>	1048 (42.0)	7859 (37.9)	0.086	1033 (43.1)	3080 (42.9)	0.005
<b>Prostatic hyperplasia</b>	760 (30.4)	6341 (30.6)	-0.006	743 (31.0)	2138 (29.8)	0.027
<b>Prostate cancer</b>	213 (8.5)	2071 (10.0)	-0.056	207 (8.6)	618 (8.6)	0.002
<b>eGFR</b>						
60-90	1569 (62.8)	13573 (65.5)		1569 (65.5)	4740 (66)	
45-59	514 (20.6)	4101 (19.8)		514 (21.5)	1558 (21.7)	
30-44	223 (8.9)	1735 (8.4)		223 (9.3)	685 (9.5)	
15-29	69 (2.8)	478 (2.3)		69 (2.9)	172 (2.4)	
<15	19 (0.8)	74 (0.4)		19 (0.8)	27 (0.4)	
missing	104 (4.2)	768 (3.7)	0.064	0 (0)	0 (0)	0.029
<b>Charlson score</b>						
0	657 (26.3)	5819 (28.1)		594 (24.8)	1894 (26.4)	
1	484 (19.4)	4067 (19.6)		463 (19.3)	1385 (19.3)	
2	512 (20.5)	3958 (19.1)		499 (20.8)	1423 (19.8)	
3	334 (13.4)	2881 (13.9)		328 (13.7)	1003 (14)	
4	219 (8.8)	1759 (8.5)		218 (9.1)	623 (8.7)	
5	141 (5.6)	1131 (5.5)		141 (5.9)	425 (5.9)	
≥6	151 (6.0)	1114 (5.4)	0.045	151 (6.3)	429 (6.0)	0.027

Table 4. Odds ratios and 95% CIs for each outcome in men matched on their propensity to receive a seven-day antibiotic prescription.

	<b>7 day prescriptions</b>	<b>3 day prescriptions</b>		
<b>Outcome</b>	<b>Number (%) of events</b>	<b>Number (%) of events</b>	<b>OR (95% CI)*</b>	<b>p-value</b>
<b>Re-consultation and re-prescription within 14 days</b>	399 (5.6)	192 (8.0)	1.52 (1.25 - 1.85)	<0.001
<b>Hospitalised for UTI within 14 days</b>	209 (2.9)	59 (2.5)	0.81 (0.61 - 1.09)	0.179
<b>Hospitalised for sepsis within 14 days</b>	18 (0.3)	4 (0.2)	0.60 (0.20 - 1.75)	0.350
<b>Hospitalised for AKI within 14 days</b>	131 (1.8)	29 (1.2)	0.62 (0.42 - 0.93)	0.021
<b>Death within 28 days</b>	96 (1.3)	36 (1.5)	1.07 (0.73 - 1.57)	0.729

\*Reference = 7 day prescription



### **Figure legends**

Figure 1. Flow of men from initial identification in the database to final cohort.

## Figures

Figure 1.

